expression of SHP1, indicating a possible role in the tumor formation in lung cancer and pointing to novel therapeutic strategies.

P2-042 BSTB: Molecular Targets Posters, Tue, Sept 4

High expression of Tenascin-C extra domains, markers of angiogenesis, in human lung cancer

Hillinger, Sven[1] Silacci, Michaela[2] Arni, Stephan[2] Brack, Simon S.[2] Weder, Walter[1] Neri, Dario[2]

[1] University Hospital, Zuerich, Switzerland [2] Swiss Federal Institute of Technology, Zuerich, Switzerland

Background: Tumor-associated extracellular matrix molecules are isoforms of proteins with a wide distribution in normal adult tissues, such as fibronectin and tenascin. Large Tenascin-C isoforms are present in almost all normal adult tissues but are upregulated in fetal, regenerating, and neoplastic tissues. In this study we investigated the expression of three tenascin isoforms in tumor tissue samples from lung cancer patients to evaluate the diagnostic and therapeutic value for clinical applications.

Methods: In total, 35 corresponding tissue samples (tumor and normal lung tissue of the same patient) have been analyzed by immunohistochemistry using three different human monoclonal antibodies to domains A1 (F16), C (G11) and D (P12). All tumor specimens have been non-small cell lung cancer types.

Results: Three isoforms G11, F16 and P12 have exhibited a very intense staining of different histological types of lung cancer. More than 80% of squamous cell carcinomas, adenocarcinomas and large cell carcinoma samples have been positively stained. None of the corresponding normal lung tissue specimens showed an expression of either tenascin domains.

Conclusions: The results show that tenascin-C isoforms are highly expressed around the neovasculature and in the stroma of the majority of non-small cell lung cancers but is undetectable in the normal lung tissue. Therefore these isoforms could represent valuable candidates for the development of antibody based biopharmaceuticals for the treatment of lung cancer.

P2-043 BSTB: Molecular Targets Posters, Tue, Sept 4

Evaluationof Eph A2 receptor expression in non-small cell lung cancer: Clinical implications and molecular charcterizations

Hirai, Kyoji; Koizumi, Kiyoshi; Kawashima, Tesuo; Yamauchi, Shigeo; Shimizu, Kazuo

Nippon Medical School, Division of Thoracic Surgery, Tokyo, Japan

The Eph proteins compromise a family of receptor tyrosine kinases that are involved in cell-cell interactions, morphogenesis and angiogenesis. Especially, EphA2 receptor has been implicated in neovascularization of various cancers with its ligand, ephrin A1. How interaction between EphA2 and ephrin A1 was concerned with intracellular signaling pathway remains to be controversial. As for cancer, other investigations has demonstrated that EphA2 is regulated by p53-family proteins, E-cadherin and ras gene. Especially, in recent reports EphA2 in non-small lung cancer may provide a promising marker to predict patients with brain metastasis.

Purpose: The purpose of this study is to determine whether EphA2 correlates with tumor progression, angiogenesis, p53 and E-cadherin mediated adhesion in non-small lung cancer.

Experimental Design: We evaluated EphA2 and ephrin A1 using immunohistochemistry in 41 cases (I:14, III:27) with long-term follow up. Additionally the relationship among EphA2 expression, MVD(microvascular density), clinicopathological parameters, and E-cadherin expression was assessed.

Results: EphA2 expression was identified in 28 cases(68.3%). Stage I cases displayed significantly lower levels than stage III cases(p=0.017). Survival curve determined by the Kaplan Meier method demonstrated that strong immunoreactivity for EphA2 was associated with overall survival (p=0.028). The MVD in EphA2 positve group was significantly higher than that in EphA2 negative group (p=0.006). In imuunohistochemical study EphA2 expression was related to loss of E-cadherin (p=0.041), but not to p53 on serial sections.

Conclusions: EphA2 expression was associated with tumor progression, angiogenesis and loss of E-cadherin.

P2-044 BSTB: Molecular Targets Posters, Tue, Sept 4

Lapatinib increases cytotoxicity against gefitinib-resistant T790M lung cancer cells by inhibiting active heterodimerization of EGFR and HER-2

Kim, Hwang-Phill[1] Kim, Tae-You[2] Han, Sae-Won[2] Im, Seock-Ah[2] Bang, Yung-Ju[2]

[1] Cancer Research Institute, College of Medicine, Seoul National University, Seoul, Korea [2] Cancer Research Institute, Seoul National University College of Medicine, Department of Internal Medicine Seoul National University Hospital, Seoul, Korea

Somatic mutations in epidermal growth factor receptor (EGFR) tyrosine kinase domain predicts the response to EGFR tyrosine kinase inhibitor (TKI) in non-small cell lung cancer (NSCLC). The emergence of acquired resistance to EGFR TKI has been recently described in patients whose tumor initially responded to gefitinib. Lapatinib is a dual inhibitor of ErbB1 (EGFR) and ErbB2 (HER-2) tyrosine kinases and has shown promising efficacy in HER-2 overexpressing breast cancer. However, its therapeutic role is not fully studied in NSCLC. Here we report that lapatinib enhances cytotoxicity against gefitinib-resistant NSCLC by blocking active heterodimerization of EGFR and HER-2. We identified a secondary T790M mutation in a NSCLC tumor with a gefitinib-sensitive L858R mutation that eventually progressed after initial response. Acquired T790M mutation conferred resistance to L858R mutant cells sensitive to gefitinib. Of the various molecules downstream of EGFR, signal transduction and activator of transcription 3 (Stat3) signaling was continuously activated in L858R/T790M cells, and the inhibition of Stat3 suppressed gefitinib-resistant cell growth. As for Stat3 inhibition, we found that lapatinib inactivated Stat3 and inhibited cell growth in gefitinib-resistant NSCLC. Finally, lapatinib was also found to block the heterodimerization of EGFR and HER-2, and this led to the inactivation of Stat3 in gefitinib-resistant T790M cells, whereas the active heterodimerization of EGFR and HER-2 was maintained when these cells were treated with gefitinib. Taken together, our data suggest that lapatinib may overcome gefitinib resistance in NSCLC. A clinical investigation of the use of lapatinib in gefitinib-resistant NSCLC is strongly warranted.